Modeling Sensitivity Analysis of Hepatitis C Virus Dynamics

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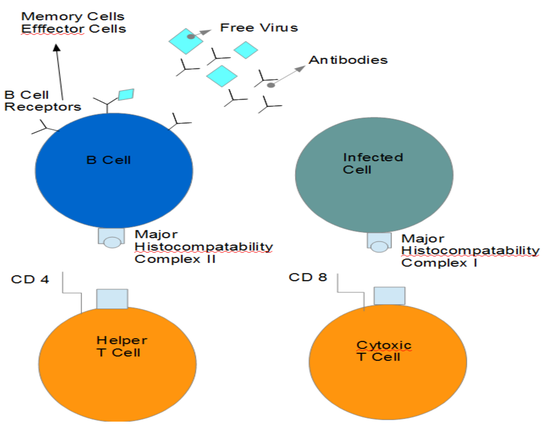
Background Information

To prevent a virus from spreading there are two types of cells used in the specific immune system response: B-lymphocytes (B cells) and T-lymphocytes (T cells). The B cell binds to the epitope of a free virus particle and draws the virus into itself. As the infected cell destroys the virus, the pieces of the virus are bound to proteins: Major Histocompatibility Complexes (MHC), specifically MHC II proteins. The MHC II bind to the pieces of the original virus and present them on the surface of the B cell in order to attract the helper T cell. The helper T cell then attaches to the B cell by the CD4 receptor and the MHC II to initiate full activation. Now fully activated, the B cell begins producing effector B cells and memory B cells through a process known as proliferation. The effector B cells, or plasma cells, start producing antibodies that neutralize the free virus particles. When a nucleated cell becomes infected, it will present a MHC I protein on its surface, which attracts cytotoxic T cells. The cytotoxic T Cells are activated by binding its CD8 receptor to the MHC I found on the infected cell. After a cytotoxic T cell has been activated, it releases enzymes into the infected cells to destroy them.



Competition Between CTL and Antibody Responses Without Therapy

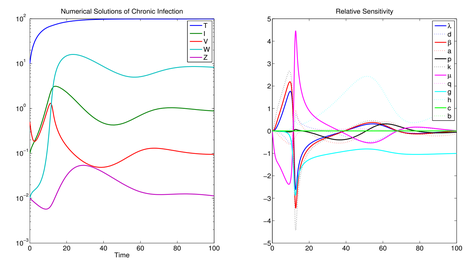
The production of CTL and antibody cells both require antigenic stimulation from infected cells, which leads to competition between the CTL and antibody populations. The model containing compartments for uninfected cells, infected cells, viral population, antibody response, and CTL response is represented by the system of ordinary differential equations originally presented by Wodarz [1].

$$\dot{T} = \lambda - dT - \beta VT \tag{1}$$
$$\dot{I} = \beta VT - aI - pIZ \tag{2}$$
$$\dot{V} = kI - \mu V - qVW \tag{3}$$
$$\dot{W} = gVW - hW \tag{4}$$
$$\dot{Z} = cIZ - bZ \tag{5}$$

If the immune system responses have the potential to develop, then three possible scenarios result from the competition between these two populations [2]. Two of these scenarios are presented in greater detail: a weak CTL response coupled with a strong antibody response resulting in chronic infection and both strong CTL and antibody responses resulting in acute infection.

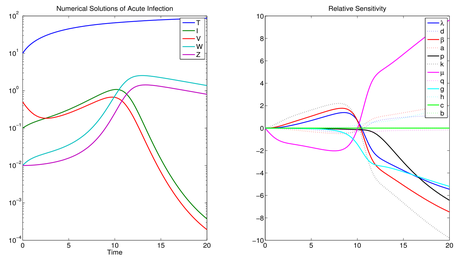
Chronic Infection Without Therapy

The first scenario examining the competition between the CTL and antibodies for antigenic stimulation involves a weak CTL response and a strong antibody response. The antibody response is able to develop fully and reduces the viral load to low levels. This scenario results in an ongoing antibody response and long term, persistent infection, or chronic infection.



Acute Infection Without Therapy

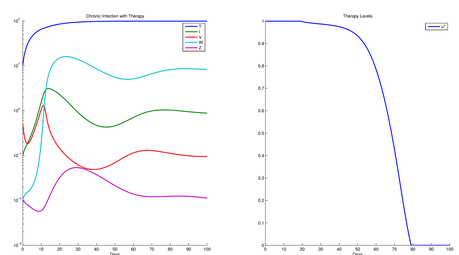
In the next scenario involving CTL and antibody dynamics, there exists a strong CTL response coupled with a strong antibody response. In this scenario both of the immune responses are able to fully develop.

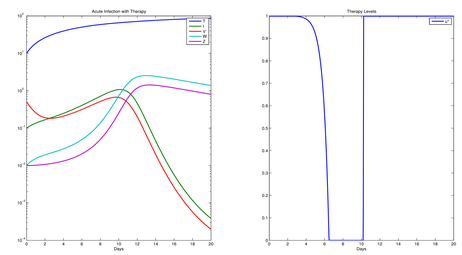


Model for CTL and Antibody Dynamics with Therapy

The use of controls on a model usually involves trade-offs between two factors competing with each other. For our model, we want to obtain the optimal dosage and time lapse to administer drug therapy, which allows for the fewest side effects and strain on the host. A control u is added to represent the optimal concentration level of therapy.

$$\dot{T} = \lambda - dT - (1-u)\beta VT \tag{6}$$
$$\dot{I} = (1-u)\beta VT - aI - pIZ \tag{7}$$
$$\dot{V} = kI - \mu V - qVW \tag{8}$$
$$\dot{W} = gVW - hW \tag{9}$$
$$\dot{Z} = cIZ - bZ \tag{10}$$





Necessary conditions and optimal control problem components: [3]

$$J(a) = \int_{t_0}^{t_1} f(t,x,u)\mathrm{d}x \tag{11}$$
$$H(t,x,u,\rho) = f(t,x,u) + \overrightarrow{\rho}\cdot\overrightarrow{g}(t,x,u) \tag{12}$$
$$\frac{\partial H}{\partial u} = 0 \text{ at } u^* \text{ (optimality condition)} \tag{13}$$
$$\rho' = -\frac{\partial H}{\partial x} \text{ (adjoint equation)} \tag{14}$$
$$\rho(t_1) = 0 \text{ (transversality condition)} \tag{15}$$

Discussion

The sensitivity analysis shows that the parameters μ, k, β, g, and λ have the largest effect on the model for chronic infection without therapy, while the parameters mu and k have the greatest effect on the model for acute infection without therapy.

Acknowledgements

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References

[1] Dominik Wodarz. *Killer Cell Dynamics: Mathematical and Computational Approaches to Immunology*. Springer Science+Business Media, LLC, New York, New York, 2007.

[2] Dominik Wodarz. *Hepatitis C Virus Dynamics and Pathology: The Role of CTL and Antibody Responses*. Journal of General Virology, 84:17431750, 2003.

[3] Suzanne Lenhart and John T. Workman. *Optimal Control Applied to Biological Models*. Chapman & Hall/CRC, Boca Raton, FL, 2007.